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Blood Relatives of Follicular Helper T Cells

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Expression of the chemokine receptor CXCR5 identifies B follicular helper T cells. In this issue of *Immunity*, Morita et al. (2011) describe a heterogeneous circulating CXCR5$^+$CD4$^+$ B cell helper population overrepresented in juvenile dermatomyositis patients.

Central memory (Tcm) and naive T cells populate T zones of secondary lymphoid organs, by virtue of expression of the chemokine receptor CCR7, L-selectin, and the integrin LFA-1. Tcm cells express IL-2 but are not necessarily polarized to T helper (Th) cell phenotypes. By contrast, effector memory T (Tem) cells are mostly polarized (Th1, Th2, and Th17 cells), secrete cytokines abundantly, have lost CCR7, and express receptors for chemokines upregulated in inflamed nonimmune parenchyma. In the past decade, B follicular helper T cells (Tfh cells) have been characterized as another type of CD4$^+$ helper T cell that specifically differentiate under the influence of the transcription factor Bcl-6.

Tfh cells exhibit effector function (help for B cells), and like other T effectors, have downregulated CCR7. Despite this, they are disproportionately located in secondary lymphoid organs rather than inflamed nonlymphoid parenchyma, but specifically within follicles rather than T zones (Campbell et al., 2003). This is due to loss of CCR7 and expression of CXCR5, the receptor for CXCL13, which is expressed constitutively by follicular stroma. CXCR5 is expressed by all mature B cells and by a small proportion of memory T cells, but the highest expression of CXCR5 is found on Tfh cells. Tfh cells secrete predominantly IL-21 and IL-4 and lesser amounts of IFN-γ and IL-17 (Yu and Vinuesa, 2010). To complicate matters further, there appears to be another population of T cells that is dependent on Bcl6, exhibits Tfh cell-like activity, but is located in extrafollicular plasma cell foci (Poholek et al., 2010). In this issue of *Immunity*, Morita et al. (2011) identify a subset of circulating CXCR5$^+$ T cells with potent B cell helper activity.

The ontogeny of Tfh cells remains unknown. It is not clear whether they differentiate from T cells shortly after priming, or whether early Th1, Th2, and/or Th17 cells can adopt follicular differentiation upon exposure to cytokines such as IL-6 and IL-21 in mice and IL-12 in humans. Their relation to CXCR5$^+$ T cells in blood also remains uncertain. These cells are absent from the blood in patients lacking ICOS, which suggests that they are related to Tfh cells (Bossaller et al., 2006). This is also supported by their abundance in mouse models characterized by excessive Tfh cell production in secondary lymphoid tissues (Simpson et al., 2010). It is possible that T cells with intermediate expression of CXCR5, shown to be potent IFN-γ and IL-17 producers (Yu and Vinuesa, 2010), could be precursors of GC Tfh cells (Figure 1). Earlier work showed that in humans, CXCR5$^+$ cells appear in the blood shortly after immunization, and CXCR5 is induced rapidly by naive and CD27$^+$ memory cells (but not CD27$^-$ Tem cells) (Schaerli et al., 2001). Compared with their tonsillar counterparts, circulating CXCR5$^+$ T cells appeared to offer little support for antibody production in coculture with autologous B cells in the absence of exogenous antigen (Schaerli et al., 2000).

Now, Morita et al. (2011) report that CXCR5$^+$ T cells from human peripheral blood provide better help to B cells than their CXCR5$^-$ counterparts. Circulating CXCR5$^+$ T cells are shown to be more effective in providing help to naive B cells at least in the presence of the superantigen staphylococcal enterotoxin B (SEB) (Morita et al., 2011). In coculture, B cells differentiate into plasmablasts and produced Ig within 6 days, in an IL-21- and ICOS-dependent manner. By contrast, CXCR5$^-$ populations are unable to induce any switched Ig and only small amounts of IgM. Furthermore, consistent with previous findings (Schaerli et al., 2001), the CXCR5$^+$ cells sampled from patients not recently vaccinated made

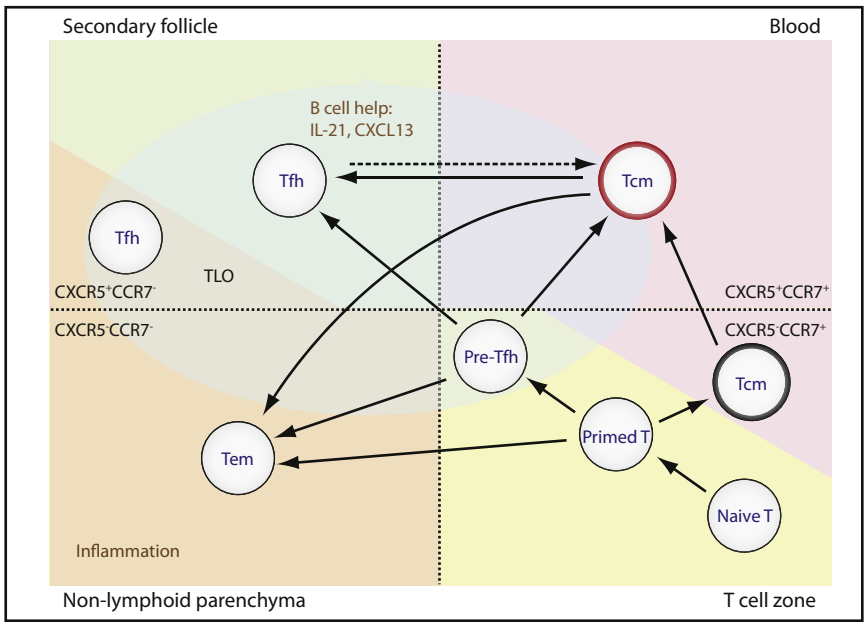

Figure 1. Model of CD4$^+$ T Cell Subsets

After priming, several T cell memory phenotypes have been identified. T cell subsets are classified according to expression of CXCR5 and CCR7 (indicated by each quadrant) and location. Tcm (T central memory), Tfh (follicular helper T), and Tem (T effector memory) cells all contain subsets capable of secreting IL-4, IFN-γ, and IL-17 to different extents. Most Tem cells are thought to have differentiated into cytokine-secreting cells and express receptors for inflammatory chemokines. Morita et al. (2011) compare CXCR5$^-$ (solid black outline) and CXCR5$^+$ (solid red outline) Tcm cells and demonstrate that the latter provide help to B cells, except for the subset that is Th1 cell-like. T cell help is associated with IL-21 expression (and CXCL13 expression). Bone fide follicular helper T cells are found in germinal centers (secondary follicles). The precursor-progeny relations between most of the effector memory T cell subsets remain unknown. pre-Tfh, Tfh cell precursors; TLO, tertiary lymphoid organs that occur in inflamed tissues and harbor ectopic germinal centers.

a more vigorous response than CXCR5$^-$ T cells to influenza virus and cytomegalovirus, reflecting a memory phenotype.

Although this study does not compare CXCR5 expression from blood and secondary lymphoid organs from the same individual, it has previously been shown that CXCR5$^+$ cells are ~100-fold more abundant in tonsil than blood (as a fraction of CD4$^+$ T cells), and within the CXCR5$^+$ subset, CXCR5 expression in tonsil is ~10-fold higher per cell than in blood (Simpson et al., 2010). Circulating CXCR5$^+$ T cells express lower ICOS than tonsillar Tfh cells and lack Bcl-6 expression (Schaerli et al., 2000; Morita et al., 2011). Morita et al. (2011) also show that CXCR5$^+$ cells express less Blimp-1 mRNA than their CXCR5$^-$ counterparts.

Morita et al. (2011) subclassify CXCR5$^+$ T cells according to receptors for inflammatory chemokines, whose expression is typical of Tem cells. A Th2 cell-like CXCR5$^+$CXCR3$^-$CCR6$^-$ subset coexpresses the transcription factor Gata-3, produces the typical Th2 cytokines—IL-4, IL-5, and IL-13—and provides help for B cell production of all Ig classes (including IgE) via IL-21 and IL-4. A third Th17 cell-like CXCR5$^+$CXCR3$^-$CCR6$^+$ subset coexpresses the Th17 cytokines IL-17A and IL-22 and provides help to B cells via IL-21 production, resulting in IgA, IgM, and IgG, but not IgE, production. A "Th1 cell-like" CXCR5$^+$CXCR3$^+$CCR6$^-$ subset expresses the transcription factor T-bet and produces IFN-γ but is distinctly unable to provide help to either naive or memory B cells.

The inability of circulating CXCR5$^+$ Th1-like cells to help B cells is puzzling. It has been known for some time that IFN-γ does not influence human isotype switching and this is clearly different in mice, in which IFN-γ is a potent switch factor for IgG2a. Mouse IgG2a binds with high affinity to activating Fc-γ receptors. Th1 cell-like CXCR5$^+$ cells express little IL-21, and this suggests that the ability to secrete IL-21 and CXCL13 distinguishes CXCR5$^+$ and CXCR5$^-$ T cell subsets. As shown in this study and reported by others, IL-21 is critical for the observed plasmablast differentiation, immunoglobulin production, and isotype switching. CXCL13 is important to attract CXCR5-expressing cells including B cells and may therefore contribute to stabilize cognate interactions.

These findings together with other recent progress still raise important questions about how immunological memory and effector responses are organized. Is immunological memory distributed or shared? In other words, if antigen reaches a lymph node via the afferent lymphatics, do Tfh cells remain localized there until the next encounter with antigen, or do they populate other secondary lymphoid organs? If each LN is the repository of a unique population of Tfh cells (distributed memory), how is information shared throughout the immune network in order to generate effector responses? Alternatively, if circulating CXCR5$^+$ T cells can become Tem cells, mediating tissue inflammation, and readily provide help to B cells, this would appear to provide a mechanism for shared memory.

These questions demand a better understanding of the precursor-progeny relations between the T cell subsets concerned. For example, do circulating CXCR5$^+$ T cells develop in a Bcl-6-dependent manner and are they therefore related to bona fide Tfh cells? Do they originate from pre or post GC Tfh cells, or both? In a manner akin to the generation of memory CD8$^+$ T cells, it is possible that circulating memory CXCR5$^+$CD4$^+$ T cells emerge both from recently activated T effector cells prior to terminal differentiation into GC Tfh cells and also, albeit to a lesser extent, after contraction of GC Tfh cells (Figure 1). Thus, upon involution of GCs and Tfh cell apoptosis, a small fraction of Tfh cells may differentiate into a circulating memory subset because of downregulation of Bcl-6 that would allow downregulation of CXCR5 and upregulation of CCR7.

Finally, recent findings point to the possibility that abundance of Tfh or Tfh-related cells in the blood can be a signature of immune-mediated pathology. In mice, it has been possible to demonstrate a causal relation between excessive Tfh cells and autoimmunity, autoantibody production, and lupus nephritis (Linterman et al., 2009). In humans with systemic lupus erythematosus, increased numbers

of circulating Tfh-like ($CXCR5^+ICOS^{hi}$ or $CXCR5^+PD\text{-}1^{hi}$) cells have been shown to associate with disease severity in a subset of patients (Simpson et al., 2010). Morita et al. (2011) show that in juvenile dermatomyositis (JDM), an autoimmune disease characterized by skin and muscle inflammation, circulating $CXCR5^+$ T cells with Th2 and Th17 cell-like characteristics are overrepresented. Because the ratio of $CXCR5^+$ $Th2^+Th17$ to Th1 cells correlates closely with clinical indicators of disease severity (rash and muscular weakness) and because these $CXCR5^+$ subsets are potent B cell helpers, this points to a possible pathogenic connection. However, the autoantibody response to JDM is not well characterized, nor is the pathogenic potential of the autoantibody response.

The plasticity of the $CXCR5^+$ T cell population described here raises the possibility that tissue recruitment causes inflammation, while autoantibody responses are an epiphenomenon mediated by recruitment of Th2- and Th17-like $CXCR5^+$ cells. If confirmed, this could provide an important insight into the high incidence of autoantibodies in autoimmune diseases, where the target autoantigens for these autoantibodies arise from the inflamed tissue, yet the autoantibodies do not appear to be pathogenic. Another possibility is that T cells that can respond to inflammatory chemokines and also provide B cell help might contribute to tertiary lymphoid tissue, which is characteristic of many autoimmune diseases (Figure 1). Much more work is required to determine whether these mechanisms hold, but the potential pay-off is identification of early markers of diseases and novel therapeutic targets.

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